Inhibitory Nerve Cell Precursors: Dosing, Safety and Efficacy

Grant Award Details

Inhibitory Nerve Cell Precursors: Dosing, Safety and Efficacy

Grant Type: Early Translational II

Grant Number: TR2-01749

Project Objective: The goal of this project is to establish the feasibility of hESC-derived medial ganglionic eminence (h-MGE) progenitor cell transplantation for the treatment of epilepsy. h-MGE differentiation will be optimized and cell dosing, safety and functional engraftment will be tested following transplantation.

Investigator:

Name:	Arturo Alvarez-Buylla
Institution:	University of California, San Francisco
Type:	PI

Disease Focus: Epilepsy, Neurological Disorders, Pediatrics

Human Stem Cell Use: Embryonic Stem Cell

Award Value: $1,564,016

Status: Closed

Progress Reports

Reporting Period: Year 1

View Report

Reporting Period: Year 2

View Report

Reporting Period: Year 3

View Report

Grant Application Details

Application Title: Inhibitory Nerve Cell Precursors: Dosing, Safety and Efficacy

Public Abstract: Many neurological disorders are characterized by an imbalance between excitation and inhibition. Our ultimate goal: to develop a cell-based therapy to modulate aberrant brain activity in the treatment of these disorders. Our initial focus is on epilepsy. In 20-30% of these patients, seizures are unresponsive to drugs, requiring invasive surgical resection of brain regions with aberrant activity. The candidate cells we propose to develop can inhibit hyperactive neural circuits after implantation into the damaged brain. As such, these cells could provide an effective treatment not just for epilepsy, but also for a variety of other neurological conditions like Parkinson's, traumatic brain injury, and spasticity after spinal cord injury. We propose to bring a development candidate, a neuronal cell therapy, to the point of preclinical development. The neurons that normally inhibit brain circuits originate from a region of the developing brain called the medial ganglionic eminence (MGE). When MGE cells are grafted into the postnatal or adult brain, they disperse seamlessly and form inhibitory neurons that modulate local circuits. This property of MGE cells has not been shown for any other type of neural precursor. Our recent studies demonstrate that MGE cells grafted into an animal model of epilepsy can significantly decrease the number and severity of seizures. Other "proof-of-principle" studies suggest that these progenitor cells can be effective treatments in Parkinson's. In a separate effort, we are developing methods to differentiate large numbers of human MGE (H-MGE) cells from embryonic stem (ES) cells. To translate this therapy to humans, we need to determine how many MGE cells are required to increase inhibition after grafting and establish that this transplantation does not have unwanted side-effects. In addition, we need simple assays and reagents to test preparations of H-MGE cells to determine that they have the desired migratory properties and differentiate into nerve cells with the expected inhibitory properties. At present, these issues hinder development of this cell-based therapy in California and worldwide. We propose: (1) to perform "dose-response" experiments using different graft sizes of MGE cells and determine the minimal amount needed to increase inhibition; (2) to test whether MGE transplantation affects the survival of host neurons or has unexpected side-effects on the behavior of the grafted animals; (3) to develop simple in vitro assays (and identify reagents) to test H-MGE cells before transplantation. Our application takes advantage of an established multi-lab collaboration between basic scientists and clinicians. We also have the advice of neurosurgeons, epilepsy neurologists and a laboratory with expertise in animal behavior. If a safe cell-based therapy to replace lost inhibitory interneurons can be developed and validated, then clinical trials in patients destined for invasive neurosurgical resections could proceed.

Statement of Benefit to California:	This proposal is designed to accelerate progress toward development of a novel cell-based therapy with potentially broad benefit for the treatment of multiple neurological diseases. The potential to translate our basic science findings into a treatment that could benefit patients is our primary focus and our initial target disease is epilepsy. This work will provide benefits to the State of California in the following areas: * California epilepsy patients and patients with other neurological diseases will benefit from improved therapies. The number of patients refractory to available medications is significant: a recent report from the Center for Disease Control and Prevention [www.cdc.gov/epilepsy/] estimates that 1 out of 100 adults have epilepsy and up to one-third of these patients are not receiving adequate treatment. In California, it is one of the most common disabling neurological conditions. In most states, including California, epileptic patients whose seizures aren't well-controlled cannot obtain a driver's license or work certain jobs -- truck driving, air traffic control, firefighting, law enforcement, and piloting. The annual cost estimates to treat epilepsy range from $12 to $16 billion in the U.S. Current therapies curb seizures through pharmacological management but are not designed to modify brain circuits that are damaged or dysfunctional. The goals of our research program is to develop a novel cell-based therapy with the potential to eliminate seizures and improve the quality of life for this patient population, as well as decrease the financial burden to the patients' families, private insurers, and state agencies. Since MGE cells can mediate inhibition in other neurological and psychiatric diseases, the neural based therapy we are proposing is likely to have a therapeutic and financial impact that is much broader. * Technology transfer in California. Historically, California institutions have developed and implemented a steady flow of technology transfer. Based on these precedents and the translational potential of our research goals, both to provide bioassays and potentially useful markers to follow the differentiation of MGE cells, this program is likely to result in licensing of further technology to the corporate sector. This will have an impact on the overall competitiveness of our state's technology sector and the resulting potential for creation of new jobs. * Stem cell scientists training and recruitment in California. As part of this proposal we will train a student, technicians, and associated postdocs in MGE progenitor derivation, transplantation, and cell-based therapy for brain repair. Moreover, the translational nature of the disease-oriented proposal will result in new technology which we expect to be transferable to industry partners for facilitate development into new clinical alternatives.